PATENT
Attorney Docket **054824-5001-01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **K.M. Burnett *et al.***	)	
	)	
Application No. **09/562,376**	)	Art Unit: **1617**
	)	
Filed: **May 1, 2000**	)	Examiner: **Abigail M. Cotton**
	)	
For: **Anhydrous Topical Skin Preparations**	)	

DECLARATION OF GEERT CAUWENBERGH UNDER 37 C.F.R. 1.132

I, Geert Cauwenbergh, declare that:

1. I am currently the Chief Executive Officer and founder of Barrier Therapeutics ("Barrier"). I am also Member and Secretary of the Board of Trustees of the Biotechnology Council of New Jersey and a Board Member of the New Jersey Center of Life Sciences and also serve as an Official Trade Advisor to the Belgian Government for Health Care in the USA. Prior to founding Barrier, I was Vice President of Technology of the Johnson & Johnson ("J&J") Consumer and Personal Care Products Companies, where I created technology platforms based on intellectual property and know-how owned by J&J and developed a business proposition around these platforms as the basis for new companies or new businesses within J&J. I also served as Vice President of Research & Development of the J&J Consumer Companies Worldwide, managing a global organization of over 100 people, with an annual budget of $35 million, and was also a member of the J&J Business Development Council. I was also the Director of the Corporate Skin Care Council of J&J, coordinating the skin care activities in the different operating groups of the Corporation. Earlier in my career, I held positions in sales, and national and international marketing and was responsible for the successful global introduction of Nizoral® (ketoconazole cream). I joined the R&D organization of the Janssen Research Foundation in 1982, where I held positions of increasing global responsibility and oversaw the development of drugs such as Sporanox®, Nizoral® Shampoo, Terazol® and topical Sufrexa®. My R&D activities have also related to the fields of psoriasis, acne, wound healing, atopic dermatitis, protozoal infections and HIV. I have authored over 100 publications and have co-authored several books. I received my Ph.D. in Medical Sciences from the Catholic University of Leuven, Faculty of Medicine. A copy of my curriculum vitae is attached as Exhibit A.

2. I have reviewed the Office Action dated July 25, 2006 and in particular the Examiner's rejection of claims 49, 51, 52, 57 to 62, 89, 90, 94, 98 to 101, 105 and 134 to 136, drawn to anhydrous gel

compositions, as obvious over the combined disclosures of U.S. Patents 5,476,852; 5,110,809; 4,214,000; and 5,292,530.

3. That as part of my duties as Chief Executive Officer of Barrier, I had those under my direction and control conduct the three below-described studies demonstrating the unexpected overall superiority of the claimed compositions of an anhydrous gel formulation of ketoconazole compared to an aqueous formulation of ketoconazole and an anhydrous gel formulation of ketoconazole and the steroid desonide. For purposes of this declaration, these three studies will be labeled as "Antiinflammatory Study", "Cumulative Irritation Study" and "Antifungal Activity Study". For each study, the tested compositions were an anhydrous topical gel product containing a combination of 2% ketoconazole and 0.05% desonide ("Combination Product"), an anhydrous topical gel product containing 2% ketoconazole ("the Ketoconazole Product"), an anhydrous topical gel product containing 0.05% desonide ("the Desonide Product") and a placebo containing just the anhydrous gel vehicle ("the Placebo Gel Vehicle"). The Cumulative Irritation Study and the Antifungal Activity Study additionally included an aqueous cream-based formulation of ketoconazole, sold commercially as Nizoral® ("the Nizoral® Product"). The exact formulations of these products are shown below:

"the Combination Product"

Component	**Weight %**
ketoconazole	2.0000
desonide	0.0500
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 33.9477
	100.0000

"the Ketoconazole Product"

Component	Weight %
ketoconazole	2.0000
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 33.9977
	100.0000

"the Desonide Product"

Component	Weight %
desonide	0.0500
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 35.9477
	100.0000

"the Placebo Gel Vehicle"

Component	Weight %
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 35.9977
	100.0000

"the Nizoral® Product"

Component	Weight %
ketoconazole	2.0
propylene glycol	
stearyl alcohol	
cetyl alcohol	
sorbitan stearate	
polysorbate	
isopropyl myristate	
sodium sulfite	
water	

A. Antiinflammatory Study

A phase III clinical trial in the United States was conducted to assess the relative antiinflammatory properties of the Combination Product, the Ketoconazole Product, the Desonide Product and the Placebo Gel Vehicle.

In this double-blind, randomized, vehicle-controlled parallel clinical study, a total of 450 patients was tested. The patients were men and nonpregnant, non-lactating women, at least 18 years of age, with clinical signs and symptoms of seborrheic dermatitis. All patients exhibited a rating score of 2 (moderate) or 3 (severe) for erythema and scaling and at least a rating score of ≥ 1 (mild) for pruritus. In addition, a baseline global evaluation score of at least 3 (moderate) for disease severity as determined by an investigator was required for study entry. The breakdown of the patient scoring is indicated below:

Parameter	Mild	Moderate	Severe
Global Evaluation	0	80%	20%
Erythema	0	85%	15%
Scaling	0	84%	15%
Pruritus	39%	51%	10%

One hundred and fifty (150) patients received the Combination Product, 150 patients received the Ketoconazole Product, 75 patients received the Desonide Product and 75 patients received the Placebo Gel Vehicle. All patients were randomized such that the studied medication was applied to the affected area(s) once daily for 14 days and followed through Day 28. Affected areas included the scalp hairline, the post-auricular area, the eyebrows, the bridge of nose, the naso-labial folds and the sternum. At each visit (days 0 (baseline), 3, 7, 14 and 28), the investigator evaluated signs and symptoms of erythema, scaling and pruritus. Each was rated on an interval scale of 0 (none) to 3 (severe), taking into account all areas of involvement. An investigator's global evaluation was conducted on days 0 (baseline), 7, 14 and 28.

The primary parameter of efficacy was the proportion of patients that were effectively treated at Day 28 of the study. Effectively treated refers to those patients who had the following assessment scores:

(i) an erythema and scaling score of 0 (none); or 1 (mild) if the baseline score was 3 and

(ii) a global status score of 0 (clear) or 1 (almost clear) if the baseline score was 3 or greater.

The Cochran-Mantel-Haenszel (CMH) row-mean scores test statistic was used to compare the treatment results between the Combination Product and the Ketoconazole Product, the Combination Product and the Desonide Product and the Combination Product and the Placebo Gel Vehicle. The CMH general associate test statistic was used to compare treatment contrasts on day 28. CMH tests were stratified by grouped study center and the Breslow-Day test was used to test for homogeneity of the odds ratio across grouped study centers.

Pre-study expectations, which were the rationale for the development of the Combination Product, were that the Combination Product would provide superior results due to the dual mechanism of action of the ketoconazole and desonide components contained in the Combination Product compared to the Ketoconazole Product (which lacked the desonide component) and the Desonide Product (which lacked the ketoconazole component). More specifically, it was rationalized that the ketoconazole would target the fungal aspect of seborrheic dermatitis while the desonide would provide relief for the inflammatory aspect (*e.g.*, erythema, scaling and pruritus) of seborrheic dermatitis. Unexpectedly, however, a post-hoc analysis of the results of the study indicated that the Ketoconazole Product was more effective than the Combination Product in alleviating not only the overall seborrheic dermatitis disease state (as shown by the attached global score graph representing day 28) but also the inflammatory factors associated with the seborrheic dermatitis (as shown by the attached combination score graph representing day 28). Both the Desonide Product and the Placebo Gel Vehicle were observed to be less effective than either the Combination Product or the Ketoconazole Product on the primary assessment time point (day 28).

There is no teaching in the cited references of these observed results – *i.e.*, that an anhydrous gel composition lacking a steroidal component is superior in alleviating inflammation compared to the corresponding composition containing a steroidal component. Further, there would be no reasonable expectation of success by a skilled artisan to formulate and use an anhydrous gel composition without a steroidal component in the treatment of a topical inflammatory disease. As stated above, the development rationale for the Combination Product was an expected superiority of the Combination Product over the Ketoconazole Product.

B. Cumulative Irritation Study

The purpose of this double-blind study was to determine the relative cumulative irritation potential of the Combination Product, the Ketoconazole Product, the Desonide Product and the Placebo Gel Vehicle using a standard and accepted testing methodology.

A total of 29 subjects was tested. The subjects were healthy men and nonpregnant, non-lactating women, at least 18 years of age, whose skin pigmentation did not interfere with the reading of the skin reactions. Absorbent patches separately containing each of the four products applied to 3 cm^2 area in an amount of 0.12 to 0.13 grams were placed on a subject's back at a designated site. Patches were prepared no more than 2 hours prior to application of the patches to the backs of the subjects. The patches remained in place for 24 hours, except on Saturdays when they remained in place for 48 hours. After 24 (or 48) hours, the patches were removed. At least 5 minutes after patch removal, the site was evaluated using a 5-point scale grading system. The sequence of applying medications, patching and reading was repeated daily (except Sundays), with application of the same four products being studied to the same sites for 21 consecutive days. Each subject was scheduled for a total of 19 visits, which resulted in 551 scheduled visits for the evaluable subject population. Only 4 of the 551 planned visits were missed, thus allowing for 547 evaluations of the four products being studied.

The grading system was as follows: "Grade 0" (no sign of irritation); "Grade 1" (slight erythema); "Grade 2" (noticeable erythema with slight infiltration); "Grade 3" (erythema with marked edema); and "Grade 4" (erythema with edema and blistering). A technician experienced and trained in reading patch test skin reactions made all evaluations. If a severe skin irritation (Grade 4) was observed at any site, no further applications were made to that site and the maximum score (Grade 4) was assigned to that site for the duration of the study. Other signs of skin reactions to the four products being studied, such as dryness, cracking, peeling, *etc.*, were noted as comments. Evaluations for all subjects were recorded by the product being studied on daily grade sheets for each grade day.

The total score for each product being studied was calculated by totaling the score for each score grade. This was accomplished by multiplying the grade by the number of times it was reported. For example, four Grade 4 scores resulted in a total score of 16. Based on this methodology, the Combination Product was the least irritating with a total score of 100, followed by the Ketoconazole Product with a total score of 119, the Desonide Product with a total score of 138, the Placebo Gel Vehicle with a total score of 219 and the Nizoral® Product of 657. These results are depicted in the attached bar graph entitled "Cumulative Irritation Comparison."

These results were unexpected for at least two reasons. First, pre-study expectations were that the Nizoral® Product would be less irritating to skin than the Ketoconazole Product because the Nizoral® Product formulation is aqueous-based while the Ketoconazole Product is alcohol-based (*i.e.*, anhydrous) and contained no steroidal component. Conventional knowledge in this art teaches that alcohol-based topical formulations are significantly more irritating to skin than water-based topical formulations.

Surprisingly, however, an analysis of the results of the study indicated that the Nizoral® Product had a cumulative irritation index of 5.5 times greater than that of the Ketoconazole Product.

A second unexpected result was the minimal observed difference between the cumulative irritation index of the Combination Product, which contains a steroidal component, and that of the Ketoconazole Product, which does not contain a steroidal component. Conventional knowledge in this art teaches that the presence of a steroid in a topical formulation serves to minimize skin irritation caused by other components of the formulation. The fact that the Ketoconazole Product differs only slightly from the Combination Product in its degree of irritation to skin is therefore surprising and very desirable, given the negative health impact associated with the use of steroids.

C. Antifungal Activity Study

The purpose of this study was to compare the relative clinical response of patients suffering from seborrheic dermatitis to the Ketoconazole Product and the Nizoral® Product. The two products being compared were not tested in the same study. Rather, there was one study comparing the Nizoral® Product with the corresponding placebo cream vehicle that was reported in the Journal of the American Academy of Dermatology 12(5), 852-856 (1985). A second study, which involved a recent comparison of the Ketoconazole Product with the corresponding placebo gel vehicle, adhered to the same protocol described for the testing of the Nizoral® Product conducted in 1985, except that the Ketoconazole Product was administered once a day while the Nizoral® Product was administered twice a day. Because the protocols for the historic first study and the second study were otherwise identical, a direct comparison between the Ketoconazole Product and the Nizoral® Product is possible. The protocol is summarized below.

A total of 37 patients suffering from seborrheic dermatitis were examined at eight sites and graded numerically at each site based on four categories on a 0 to 3 grading scale. A score of "0" indicated clear skin, "1" indicated a mild disease state, 2" indicated a moderate disease state and "3" indicated a severe disease state. The eight examined sites were scalp, hairline, eyebrows, bridge of nose, nasolabial folds, ear canal, posterior aspect of ear and chest. The four categories evaluated were erythema, scaling, papules and pruritus. The maximum score obtainable at each visit was 96 (*i.e.*, a score of 3 multiplied by 4 different categories at 8 sites).

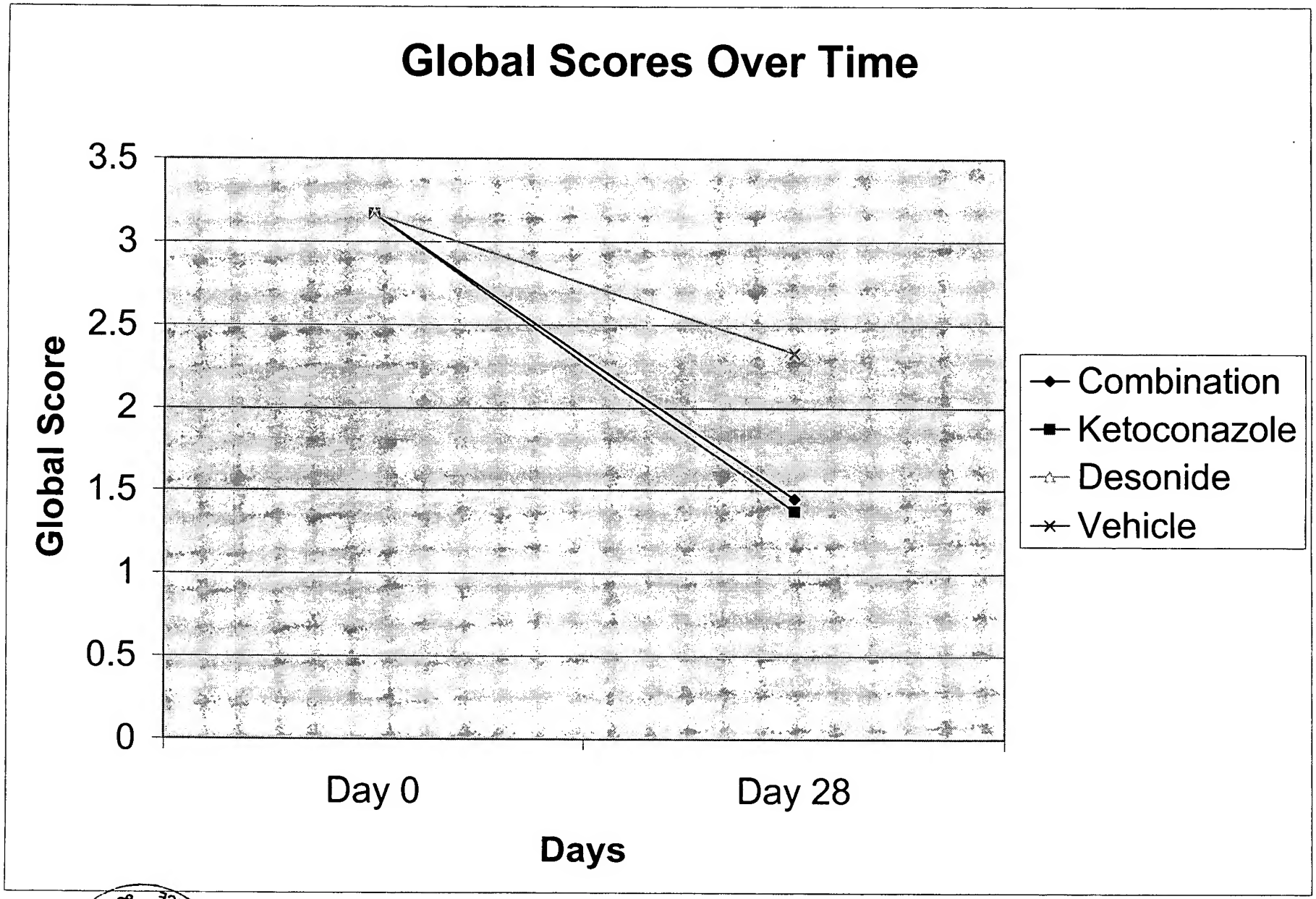
Swabs were obtained for visual assessment of *Malassezia ovalis* (*Pityrosporum ovale*) from the frontal scalp, occipital scalp, right ear and face (eyebrows, bridge of nose and nasolabial folds). The patients were assigned either the Nizoral® Product or the Ketoconazole Product in a randomized fashion and were instructed to apply the assigned product to the scalp, face and ears, twice a day for the Nizoral® Product and once a day for the Ketoconazole Product. No other topical or oral medications considered as

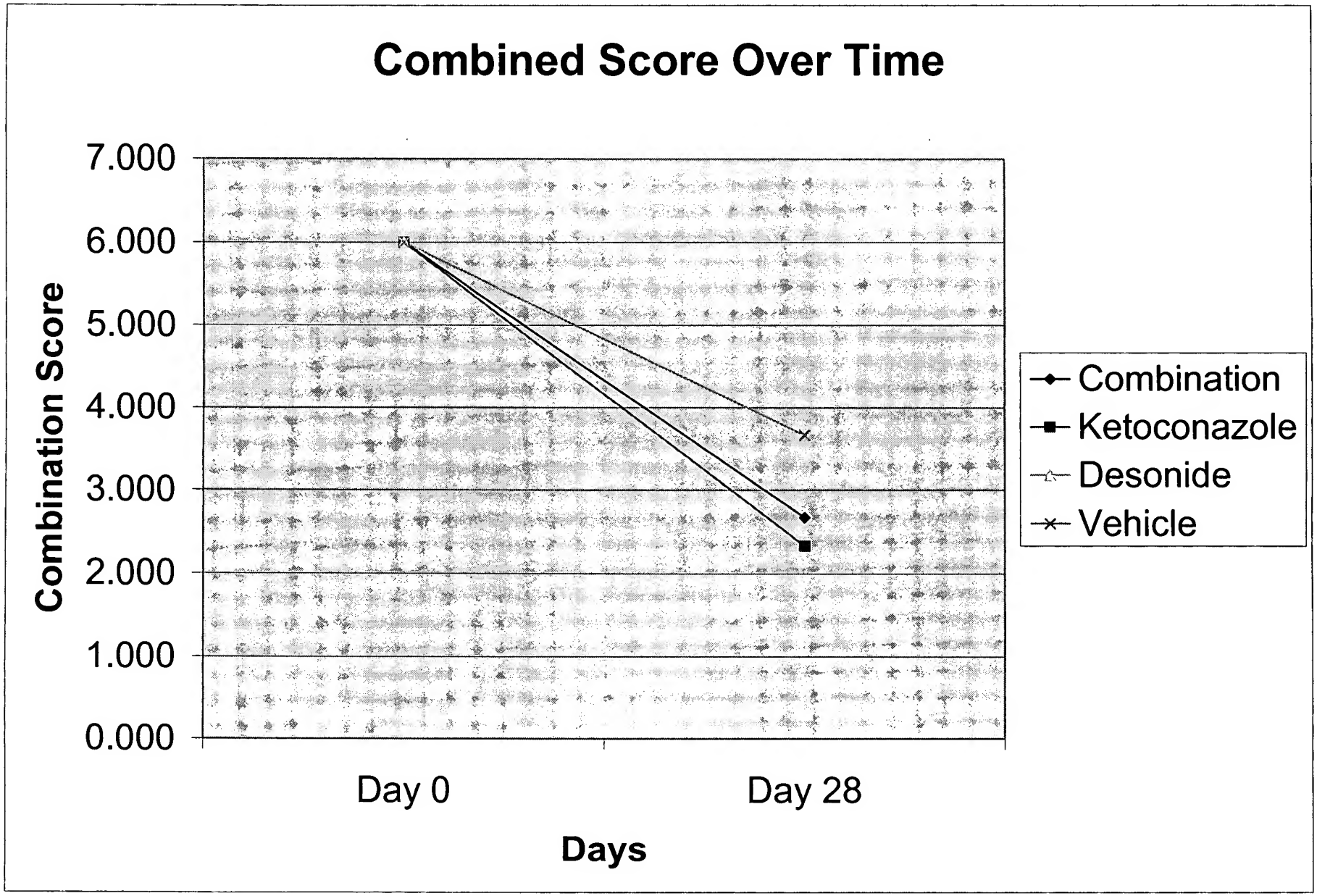
therapy for seborrheic dermatitis were allowed for the duration of the study. The patients were evaluated at two weeks. On each visit, the eight sites were graded numerically for the four categories. The patients received a global evaluation at the end of the study. The global evaluations ranged from total clearing (95-100% improvement), good (75-95% improvement), fair (50%-75% improvement) and poor (less than 50% improvement). Unexpectedly, the Ketoconazole Product had a global score after two weeks of 68.90% under a once-a-day regimen of administration compared to a global score of 49.50% for the Nizoral® Product under a twice-a-day regimen of administration. These results are depicted in the attached bar graph entitled "Reduction in Symptom Severity of Seborrheic Dermatitis." Such a result suggests that the anhydrous gel formulation of the Ketoconazole Product provides enhanced penetration of the ketoconazole through the epidermis compared to the aqueous cream formulation of the Nizoral® Product. The effect of this enhanced penetration is sufficiently significant such that once-daily dosing of the Ketoconazole Product over a two-week period results in a more effective treatment of seborrheic dermatitis than twice-daily dosing of the Nizoral® Product over the same time period.

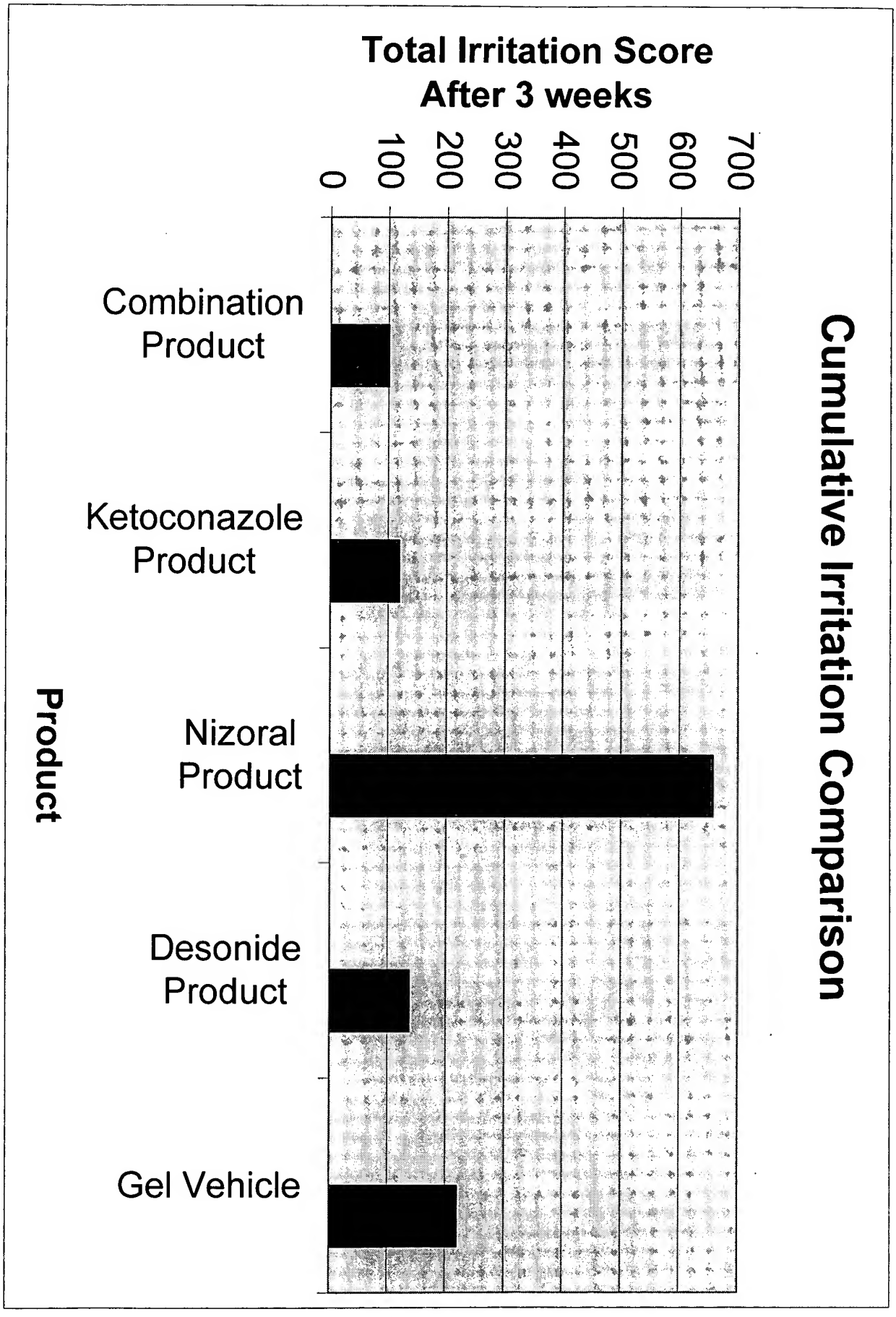
4. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

October 13, 2006
Date

Geert Cauwenbergh, Ph.D.




Combined Score Over Time
Combination Score
7.000
6.000
5.000
4.000
3.000
2.000
1.000
0.000
Day 0
Day 28
Days
Combination
Ketoconazole
Desonide
Vehicle


Cumulative Irritation Comparison
Total Irritation Score
After 3 weeks
0
100
200
300
400
500
600
700
Product
Combination Product
Ketoconazole Product
Nizoral Product
Desonide Product
Gel Vehicle

Reduction in Symptom Severity of Seborrheic Dermatitis